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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,462	10/18/2005	Gordon Weingarten	PG4894USW	4839

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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 10/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/524,462	WEINGARTEN ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-14,20 and 23-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-9,11,14,20,25-31 and 34-40* is/are allowed.

6)☒ Claim(s) *12,13,32,33 and 41-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/3/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response, which included addition of new claims 41-46 and amendment claims 12 and 13, filed on 8/3/2006, is made of record. Claims 1-9 and 11-14, 20 and 23-46 are now pending. In view of applicants' response, the following apply.

Information Disclosure Statement

References cited in the Information Disclosure Statement, filed on 8/3/2006, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12,13, 41 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claims 12 and 13 are indefinite as it is not clear as to what protected derivative being referred to therein and how one having arrive at a compound of formula I then thereafter and if necessary perform deprotection recited therein. First of all, it is not clear how is R^1-X-H is protected. Careful analysis of choices of R^1 and X does not reveal how would one protect R^1-X-H (note R^1-X-H is also H_2O). Secondly, the process of claims 12 and 13 arrive at the final product-compound of formula I or formula IA, but not a protected form as recited therein. Furthermore, the choices of other varible groups appear to include esters and carbamates, which are the conventional protecting groups.

It is not clear how would one distinguish between these groups and undefined protecting groups.

2. Recitation of "interconverting the compound of formula (I) into another compound of formula (I)" in claim 41 and "interconverting the compound of formula (IA) into another compound of formula (IA)" in claim 42, renders these claims vague and unclear as to what is intended. If step A to produce compound of formula (I) what is not included in this compound of formula (I) that is being transformed in subsequent step B. Similarly, the product of claim 12 or 13 is not a derivative of the compound of formula I or IA and hence the need for the said conversion is unclear.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 24, 32, 33 and 43-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating pain due to headache or arthritis or treating dysmenorrhoea, does not reasonably provide enablement for treating any or all acute or chronic pain originating from various diseases generically embraced in the claim language. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Following reasons apply.

As recited, claims 23, 24, 32 and 33 are reach through claims. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic

functionality and thereby reach through any or all diseases, disorders or conditions for which they lack written description and enabling disclosure in the specification. In the instant case, because of the inhibition of COX-2 activity shown by compound formula I, it is recited that instant compounds are useful for treatment of any or all pain caused by any or all diseases including neurodegenerative diseases and cancers, for which there is no adequate written description and enabling disclosure in the instant specification.

The scope of the claims includes treating any or all pain arising from various diseases and disorders as mediated by COX-2 for which there is no enabling disclosure. In addition, the scope of these claims includes treating acute and chronic pain of any origin and would include lower back and neck pain, headache, toothache, sympathetically maintained pain, neuropathic pain syndromes include: diabetic neuropathy; sciatica, non-specific lower back pain; multiple sclerosis pain, fibromyalgia, HIV-related neuropathy neuralgia, such as post-herpetic neuralgia and trigeminal neuralgia; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions. These conditions are difficult to treat and although several drugs are known to have limited efficacy, complete pain control is rarely achieved. The symptoms of neuropathic pain are incredibly heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical

hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia), etc., which are not adequately enabled solely based on the inhibiting COX-2 activity of the compounds provided in the specification at pages 1-8 and 24. The instant compounds are disclosed to have inhibiting COX-2 activity and it is recited that the instant compounds are therefore useful in treating any or all acute and chronic pain where COX-2 activity is implicated, for which applicants provide no competent evidence. Furthermore, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. The scope of the claims involves all of the thousands of compounds of instant claims as well as the thousand of diseases causing pain both acute and chronic embraced by the terms inflammatory diseases, non-vascular syndromes etc

Inflammation is a process that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, leukotrienes, cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally. There is a vast range of forms that it can take,' causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There are hundreds such

diseases, which have fundamentally different mechanisms and different underlying causes. Thus, the scope of claims is extremely broad.

No compound has ever been found to treat all types of pain. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits.

Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds.

The state of the art at the time of instant invention is indicative of the requirement for undue experimentation. See Stichtenoth et al., Drugs, 63(1): 33-45, 2003 and Hochberg MC., Am. J. Manag. Care., 8(17Suppl):S502-517, 2002.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence

or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating any or all pain from various diseases and disorders that require inhibiting COX-2 activity.

2) The state of the prior art: Publications expressed that treating acute and chronic pain caused by diseases or disorders by the inhibition of COX-2 is still exploratory. See Stichtenoth et al., and Hochberg MC., cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating any or all pain arising from any or all diseases or disorders of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all pain and the state of the art is that the effects of inhibiting COX-2 activity are unpredictable and at best limited to modulation of rheumatoid arthritis.

6) The breadth of the claims: The instant claims embrace any or all pain due to diseases and disorders related COX-2 activity.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of receptor-ligand interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of pain arising from diseases by the instant compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

This rejection is same as made in the previous office action but now limited to reach through claims 23, 24, 32 and33 as well as newly added claims 43-46 for which applicants have not provided supporting non-patent literature.

Applicants' argument to overcome this rejection is not persuasive. First of all, as noted above these claims are reach through claims. Based on the mode of action of the instant compounds as COX-2 inhibitors, theses claims reach through treating any or all acute and chornic pain for which there is no objective enablement both in the specification and prior art.

References discussed by the applicants also does not lend support , contrary to applicants' urging, treating any or all acute and chronic pain. For example, the celebrex literature provided by the applicants clearly indicates that the celebrex can be used for arthritis pain. Applicants' have extrapolated this to treating all chronic and acute pain. The said literature does not say so and celebrex is in the market for quite some time. Still it has not found such wide application of treating any acute or any chronic pain. Same true for Stichtenoch et al., The article does show that any or all acute and chronic pain can be treated with COX-2 inhibitors. The article clearly shows use of the said compounds for arthritis.

As for back pain and neck pain embraced in claims 43-46, applicants' are urged to provide a reference supporting such a use of COX-2 inhibitors.

Based on these considerations, this rejection is deemed as proper and is maintained.

Allowable Subject Matter

Claims 1-9, 11, 14, 20, 25-31 and 34-40, barring finding of any prior art in a subsequent search, are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

10/14/2006